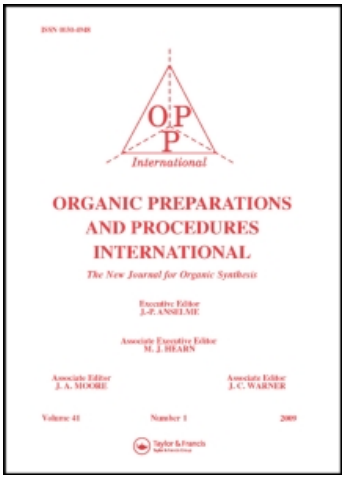

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OPTIMIZED SYNTHESIS OF SOME γ,γ-DISUBSTITUTED ALLYLAMINES

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OPTIMIZED SYNTHESIS OF SOME γ,γ-DISUBSTITUTED ALLYLAMINES

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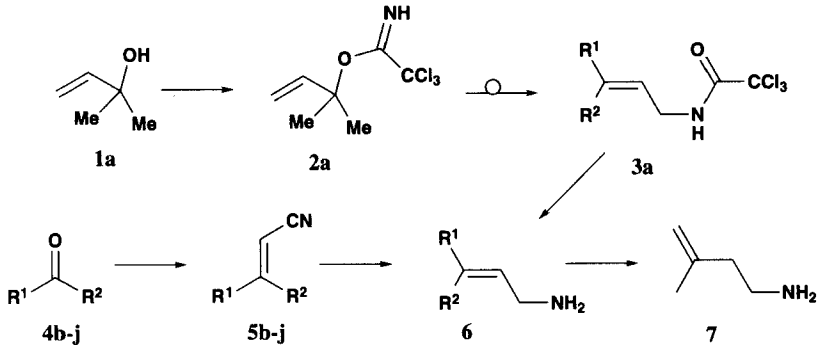
The structural motif of γ,γ-disubstituted allylamines is present in natural products such as the cytokinins zeatin (**8e**)[1] and N-(3-methyl-2-butenyl)adenine.[2] The structure also occurs in various antiviral[3] and antiallergic[4] agents. The main purpose of the present work was to develop efficient methods of synthesis for gram to kilogram amounts of various allylamines used as pharmaceutical building blocks.

Although numerous procedures for the synthesis of allylamines have been reported, some lack experimental details or are not suitable for scale-up. In addition, they involve multi-step synthesis, produce low yields or use toxic or expensive reagents. Thus, the Gabriel synthesis suffers from poor availability of the corresponding allyl halides. The palladium(0) catalyzed nucleophilic substitution of allyl acetates with azide ion followed by triphenylphosphine reduction uses rather large amounts of Pd reagents which cannot be recycled easily.[5] In the case of asymmetrically substituted products, laborious separation of the geometrical isomers is necessary.[6] To our knowledge, the reduction of acrylonitriles has been used only for the preparation of γ,γ-dimethylallylamine (**6a**) and of 4-amino-2-methyl-2-buten-1-ol (**6e**). The rearrangement of trichloroacetimidates of α,α-disubstituted allyl alcohols to γ,γ-disubstituted allyl acetamides was first developed by Overman.[7] The major drawback of similar cobalt catalyzed rearrangements, described by Nayyar *et al.*[8] is the contamination of the resulting allyl amides with substantial amounts of allyl esters.

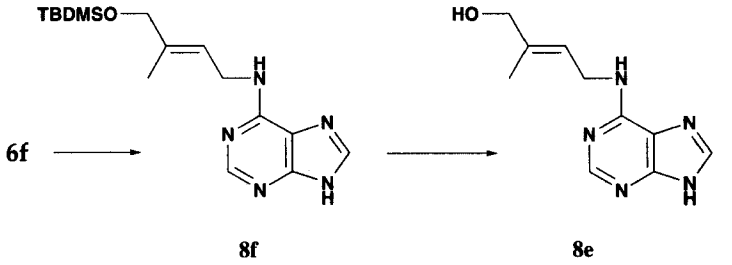
Previous synthesis of γ,γ-dimethylallylamine (**6a**) suffer from difficulties in isolation, purification[9], isomerization[10] (e.g. to **7**) and relatively low yields[11]. Similarly, earlier preparations of **6e** involve expensive reagents[12], multi-step and complicated sequences and low yields[13]. We now report optimized procedures for allylamines **6a-k** (Scheme 1) and the conversion of **6f** to **8f** and **8e** (Eq. 1).

The addition of commercially available 1,1-dimethylallyl alcohol (**1a**) to trichloroacetonitrile and rearrangement of the crude imidate (**2a**) produced an improved yield (71-82%) of pure **3a**. Compound **6a** was isolated as the maleate with an 80% yield by hydrolysis of the amide, thus giving an overall yield of 57-66% from **1a**. In our hands cyclic alcohols **1b,c**[14] failed to react with trichloroacetonitrile in useful yields, although the formation of the imidate **2c** was reported in a 57% yield (Eq. 2).[7] Variation of bases (KH, KH and 4-dimethylaminopyridine, NaH, NaOMe) and solvents



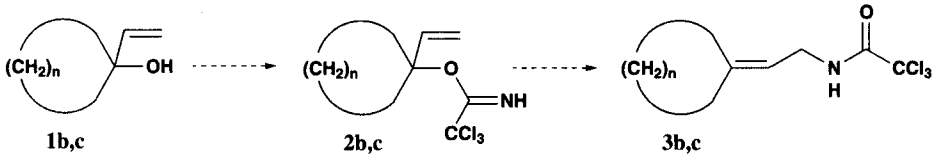
a) $R^1 = R^2 = Me$, b) $R^1 = R_2 = -(CH_2)_4-$, c) $R^1 = R^2 = -(CH_2)_5-$, d) $R^1 = R^2 = -(CH_2)_2-CH(CMe_3)-(CH_2)_2$,
e) $R^1 = CH_2OH$, $R^2 = Me$, f) $R^1 = CH_2O$-TBDMS, $R^2 = Me$, g) $R^1 = CH_2O$-THP, $R^2 = Me$,
h) $R^1 = R^2 = -(CH_2)_2-NH-(CH_2)_2-$, i) $R^1 = R^2 = -(CH_2)_2-NBoc-(CH_2)_2-$,
j) $R^1 = R^2 = -(CH_2)_2-NTrityl-(CH_2)_2-$

Scheme 1



(1)

(Et_2O, THF, and mixtures thereof) resulted in low-yield conversion to **2c** only. Alcohol **1b** gave a 5% conversion to imidate **2b** which rearranged to the amide **3b** on work-up.

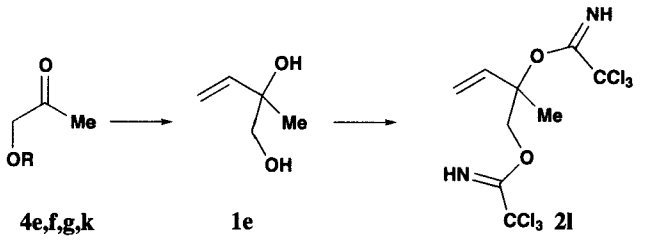


(2)

b) n = 4, c) n = 5

In order to utilize this route for the preparation of **6e**, a series of O-protected hydroxyacetones (**4f, 4g, 4k**) was prepared (Eq. 3). In spite of the stability of the protecting groups towards methylmagnesium bromide, none of the protecting groups was stable to vinylmagnesium bromide; however, conversion of hydroxyacetone to **1e** using an excess of vinylmagnesium bromide resulted in a 55% yield. Since an attempt to selectively protect the primary alcohol of **1e** using benzyl bromide and sodium hydride in DMF at -40°[15] failed, **1e** was converted to the *bis* imidate **2l** which did not rearrange, but slowly underwent cleavage of the imidate groups. As cobalt-catalyzed rearrangement[8]

of **1e** using acetic anhydride in acetonitrile also failed, no further attempts to synthesize **6e** by rearrangement reactions were made.



4e,f,g,k **1e** **2l** (3)

e) R = H f) R = TBDMS k) R = TBDPhS

Hydride reagents reduce acrylonitriles to saturated amines,[1b,16] allylamines,[1b,11,17] acroleins[18] and saturated aldehydes[19] or nitriles[1b,17b,20] depending on the type of reagents used and on the specific reaction conditions. For the preparation of allylamines, the reagent of choice is lithium aluminium hydride (LAH) in ethyl ether. $NaBH_4/CoCl_2$ gives saturated amines[16] while Dibal-H led to saturated or unsaturated aldehydes depending on the amount of reagent used with **5c** as substrate. The use of LAH in THF instead of ether resulted in the reduction of the double-bond. The best yields of allylamines were achieved by very slow addition of the nitrile to the hydride solution in ethyl ether at room temperature. At lower temperatures, substantial amounts of oligomeric products, emanating from a Michael reaction, were obtained because the reduction was not sufficiently rapid to consume the nitrile to prevent attack by the amine already formed. The same side-reaction occurred when the addition was too rapid or when the hydride was added to the nitrile. In boiling ether, saturated amines were the main products. The optimum molar ratio of nitrile to $LiAlH_4$ proved to be 1:0.9. Larger ratios of hydride gave substantial amounts of saturated products, while lower ratios gave products contaminated with aldehydes (after aqueous workup) even if reaction times were doubled. The use of AlH_3 (prepared *in situ* from $LiAlH_4$ and H_2SO_4) gave better yields with some amines, while the use of $LiAlH_4/AlCl_3$ complex failed to improve yields and complicated the work-up. The results are summarized in Table 1.

TABLE 1. Comparison of Reducing Agents [a]

Product	$LiAlH_4$	$LiAlH_4/AlCl_3$	AlH_3
6a	27%	32%	–
6b	55%[b]	–	67%[b]
6c	67%[b]	65%[b] (80%)	57%[b] (80%)
6d	41%[b] (80%)	–	–
6f	40%	42%	51%
6g	(45%)	–	–
6j	30%	–	–

a) crude yields are given in parentheses. b) as maleate.

For the synthesis of **6e**, two different protecting groups were used.[1b,16] Although in our hands the yields of the reduction steps were comparable, we prefer the *t*-butyldimethylsilyl-group (TBDMS-), because **6f** can be distilled, while **6g** is difficult to purify. Although Chen[16] reported that deprotection of **6f** by sulfuric acid in methanol gave **6e** as a sulfate in quantitative yield, we were not able to obtain a crystalline sulfate or other suitable salts. As the free amine **6e** could not be purified in acceptable yields, we used either the protected amine **6f** for subsequent substitution reactions and cleaved the protecting group later or the crude deprotected product, which was suitable for synthetic purposes. Attempts to reduce **5i** to **6i** at room temperature failed because of the poor solubility of the substrate in ether. Continuous extraction of the substrate under reflux resulted in cleavage of the Boc-group and reduction of the double bond. The addition of small amounts (5 to 10%) of THF or 1,2-dimethoxyethane to dissolve the substrate in ether resulted in reduction of the double bond. This problem was overcome by the use of the trityl protective group (**5j**) instead of **5i**.

The required acrylonitriles (**5**) were prepared via Horner-Emmons reactions from the corresponding ketones either according to Marshall *et al.*[21] in 1,2-dimethoxyethane, or according to Villieras and Rambaud [22] in aqueous solution using potassium carbonate as a base. Hydroxyacetone (**4e**) in both procedures gave the *trans*-product (**5e**) exclusively. This result was verified by ^{1}H-NMR of the reaction mixture and GC of the distilled product. By contrast, the O-protected ketone **4f** gave a 2:1 ratio of *trans*-(**5f**) to *cis*-product. These isomers could be separated by spinning-band column distillation. Reduction of the *cis*-nitrile, under conditions which had been successful for the *trans*-product **5f**, did not result in any detectable amounts of *cis* amine due to decomposition. The tetrahydropyranyl-protected nitrile **5g** was synthesized as described by Letham *et al.*[1b]

The amines described in this work showed high nucleophilic reactivity. Thus reaction of **6f** with 6-chloropurine was carried out by a standard procedure[23] resulting in a 70% yield of **8f**. Further examples using various thieno[2,3-d]pyrimidines and thieno[3,2-d]pyrimidines will be reported elsewhere.

EXPERIMENTAL SECTION

Mps. were determined on a Kofler melting point apparatus and are uncorrected. Elementary analyses were performed at the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna (Mag. J. Theiner). ^{13}C- and ^{1}H-NMR-spectra: Bruker AC 200 (^{1}H: 200.13 MHz, ^{13}C: 50.47 MHz), 5 mm dual ^{1}H/^{13}C-VT-probe head at 300 K; solvent: DMSO-d_6 and $CDCl_3$, respectively; δ-values are given in ppm, internal standard TMS; IR-spectra: Perkin Elmer Grating Infrared Spectrometer Type 377; absorptions in cm^{-1}. GC Analyses: Carlo-Erba Fractovap Series 2150 using a Chrompack SE 54 column with a split 1:50 at a flowrate of 1 mL He/min. Temperature program used: 2 min at 60°; 15°/min to 180°; temperature kept constant for 5 min. THF, ethyl ether and 1,2-dimethoxyethane (DME) were freshly distilled from sodium and benzophenone immediately before use. All reaction using dry solvents were carried out in a dry nitrogen atmosphere.

2,2,2-Trichloroethanimidic Acid (1,1-dimethyl-2-propenyl)ester (2a).- A sodium hydride dispersion (60% in paraffin, 10 g, 250 mmol) was washed with petroleum ether (40-65°, 3 x 10 mL) and

suspended in 50 mL of dry THF. A solution of 100 g (1.16 mol) of 2-methyl-3-buten-2-ol (**1a**) (Aldrich) in 100 mL of dry THF was added dropwise at a temperature below 20°. After stirring for an additional hour, the solution was added to 167.6 g (1.16 mol) of trichloroacetonitrile in 1 L of dry ether over the course of 20 min. at -5 to +5°. Stirring at this temperature for 1 h and evaporation of the solvent yielded 292.3 g of a brown oil. The crude product containing 90% of **2a** (estimated by NMR) was used for the next step without further purification. ^{1}H NMR ($CDCl_3$): δ 1.66 (s, 6H), 5.12 (dd, J_{cis} = 8Hz, J_{gem} = 0.5Hz, 1H), 5.28 (dd, J_{trans} = 18Hz, J_{gem} = 0.5Hz, 1H), 6.16 (dd, J_{trans} = 18 Hz, J_{cis} = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 25.8 (q), 67.7 (s), 84.0 (s), 113.1 (t), 141.8 (d), 159.9 (s). IR: (film) ν(cm^{-1}) 3341, 2982, 1663, 1321, 964, 868, 797, 645.

***N*-(3-Methyl-2-butenyl)-2,2,2-trichloroacetamide (3a)**.- Crude **2a** was refluxed in 1.5 L toluene for 1 h and the solvent evaporated. The crude product (276.1 g) was purified by distillation through a short column (87-90°/0.015 mm Hg) to yield 190.0 g of **3a** (71%) (lit.[24] 60%) as colorless crystals, mp. 39-41°, lit.[24] 40-41°. The same reaction carried out at 1/10 of the scale described, gave a yield of 82%. ^{1}H NMR ($CDCl_3$): δ 1.68 (s, 3H), 1.74 (s, 3H), 3.93 (dd, 2H), 5.22 (dt, 1H), 6.70 (b, 1H). ^{13}C NMR ($CDCl_3$): 17.8 (q), 25.5 (q), 39.3 (t), 92.5 (s), 118.0 (d), 138.3 (s), 161.5 (s). IR: (KBr) ν(cm^{-1}): 3315, 2935, 1699, 1531, 1443, 1379, 1256, 1196, 1055, 824, 731, 652.

Anal. Calcd. for $C_7H_{10}Cl_3NO$: C: 36.47, H: 4.37, N: 6.08. Found: C: 36.18, H: 4.12, N: 6.14

2-Cyclopentylidenacetonitrile (5b).- Cyanomethylphosphonic acid diethyl ester[25] (8.84 g, 50 mmol), 4.37 g (52 mmol) of **4b** and 11.1 g (80 mmol) K_2CO_3 were dissolved in 40 mL of water and stirred at 80° for 2.5 h. After cooling to room temperature, the reaction mixture was extracted with ethyl acetate (2 x 30 mL), the combined organic layers were dried using Na_2SO_4 and charcoal, filtered, and evaporated to yield 4.70 g (88%) of **5b** as a pale yellow liquid, bp. 90-92°/15 mm Hg (lit.[26] 116°/55 mm Hg). ^{1}H NMR ($CDCl_3$): δ 1.7-1.85 (m, 4H); 2.35-2.55 (m, 4H); 5.20 (t, J = 2,4Hz, 1H).

2-Cyclohexylidenacetonitrile (5c).- Cyanomethylphosphonic acid diethyl ester[25] (35.4 g, 200 mmol), 20.4 g (208 mmol) of **4c** and 44.3 g (320 mmol) of K_2CO_3 were suspended in 320 mL of water and stirred for 90 min. at 80°. After cooling, the reaction mixture was extracted with ethyl acetate (3 x 120 mL). The combined organic layers were extracted with brine (2 x 50 mL), dried (Na_2SO_4) and evaporated. The crude product was distilled using a short column, yielding 17.4 g (72%) of **5c** as a colorless liquid, bp. 87-89°/13 mm Hg. ^{1}H NMR ($CDCl_3$): δ 1.5-1.75 (m, 6H); 2.20 (t, 2H); 2.45 (t, 2H,); 5.00 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 25.3 (t), 27.3 (t), 27.7 (t), 32.1 (t), 35.7 (t), 91.7 (d), 116.7 (s), 168.5 (s).

2-(4-*t*-Butylcyclohexyliden)acetonitrile (5d).- A sodium hydride dispersion in paraffin (60%, 2.00 g, 50 mmol) was rinsed with petroleum ether (40-65°, 3 x 40 mL), suspended in 80 mL of dry DME and cooled in an ice-bath. Then 8.84 g (50 mmol) of cyanomethylphosphonic acid diethyl ester[25] in 60 mL of DME were added at a temperature not exceeding 5°. After additional stirring at 10° for 10 min 7.70 g (50 mmol) of **4d** in 10 mL of DME were added and the temperature adjusted to 5-10°. The reaction mixture was allowed to warm up to room temperature. After stirring overnight, the mixture was cooled to 0° and 90 mL of cold water was added dropwise. After 1h the mixture was extracted with ether (3 x 80 mL) and ethyl acetate (2 x 60 mL). The combined organic layers were dried (Na_2SO_4)

and evaporated. The semi-crystalline residue was Kugelrohr-distilled (100°/0.2 mm Hg) to yield 6.30 g (71%) of colorless crystals, mp. 49-54°. ^{1}H NMR ($CDCl_3$): δ 0.82 (s, 9H); 1.0-1.25 (m, 3H); 1.9-2.25 (m, 4H); 2.42 (m, 1H); 2.99 (m, 1H); 5.01 (s, 1H).

Anal. Calcd. for $C_{12}H_{19}N$•0.1 H_2O: C: 80.48, H: 10.81, N: 7.82. Found: C: 80.48, H: 10.52, N: 7.92

***E*-4-Hydroxy-3-methyl-2-butenenitrile (5e)**.- A mixture of 100 g (0.565 mol) cyanomethylphosphonic acid diethyl ether[25], 45.0 g (0.607 mol) of **4e** and 150.0 g (1.09 mol) of potassium carbonate in 1 L of water was stirred at 90° for 1.5 h. The cooled reaction mixture was extracted with ethyl acetate (4 x 200 mL), the combined organic layers were dried using Na_2SO_4 and charcoal and evaporated to yield 46.0 g of **5e** as a yellow liquid (>90% pure according to GC; 70%), which can be used without further purification or purified by Kugelrohr-distillation, bp. 75-77°/0.001 mm Hg. Thus 13.0 g of the crude product yielded 10.2 g of pure **5e**. On larger scales, the yield of the distilled product decreases due to partial oligomerization. ^{1}H NMR ($CDCl_3$): δ 1.96 (s, 3H); 3.15 (b, 1H); 4.11 (s, 2H); 5.50 (s, 1H).

***E*-4-(*t*-Butyldimethylsilyloxy)-3-methyl-2-butenenitrile (5f)**.- A mixture of 10.00 g (103 mmol) of **5e**, 17.1 g (113 mmol) of *t*-butyldimethylsilyl chloride and 400 mg (3.2 mmol) of 4-dimethylaminopyridine in 100 mL dry dichloromethane was treated dropwise with 12.1 g (120 mmol) of triethylamine in 50 mL of dry dichloromethane. After stirring for 6 h at room temperature 200 mL of ether were added and the reaction mixture was extracted with 120 mL of water followed by 100 mL of brine. The aqueous layers were re-extracted with 40 mL of ether and the combined organic layers were dried (Na_2SO_4) and evaporated. The crude product (22.5 g) was distilled (54-55°/0.002 mm Hg) to yield 19.0 g (88%) of **5f** as colorless liquid. ^{1}H NMR ($CDCl_3$): δ 0.07 (s, 6H); 0.93 (s, 9H); 1.97 (d, J = 0.6 Hz, 3H); 4.16 (m, J = 0.8 Hz, 2H); 5.52 (m, 1H). ^{13}C NMR ($CDCl_3$): δ -3.8 (q); 17.0 (q); 20.0 (s); 25.6 (q); 65.4 (t); 93.2 (d); 117.0 (s); 162.7 (s).

4-(Tetrahydro[2*H*]pyran-2-yloxy)-3-methyl-2-butenenitrile (5g).- A mixture of 3.00 g (31 mmol) of **5e** and 3,4-dihydro[2*H*]pyran (distilled from $LiAlH_4$) was treated with a few crystals of *p*-toluenesulfonic acid while stirring resulting in a delayed exothermic reaction. Then the mixture was refluxed for 30 minutes. The solution was allowed to cool to 60°, treated with 0.5 g of dry potassium carbonate, stirred for 10 min and filtered. The product was distilled (70-75°/0.04 mm Hg) to yield 5.2 g (93%) of **5g** as colorless liquid. ^{1}H NMR ($CDCl_3$): δ 1.40-1.90 (m, 6H); 2.02 (m, 3H); 3.45-3.5 (m, 1H); 3.7-3.5 (m, 1H); 3.97 (d, J = 16 Hz, 1H); 4.23 (d, J = 16 Hz, 1H), 4.64 (m, 1H), 5.51 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 17.7 (q); 18.9 (t), 25.0 (t); 30.1 (t); 62.0 (t); 68.7 (t); 94.1 (d); 98.1 (d); 116.7 (s); 160.3 (s).

2-Piperidin-4-ylidenacetonitrile (5h).- A solution of 9.00 g (59 mmol) of 4-piperidinone hydrochloride-hydrate, 10.45 g (59 mmol) of cyanomethylphosphonic acid diethyl ester[25] and 20.73 g (150 mmol) of K_2CO_3 in 120 mL of water was refluxed for 1 h and extracted with toluene (2 x 20 mL). The aqueous layer was saturated with K_2CO_3 and extracted with ethyl acetate (10 x 25 mL). The combined EtOAc-layers were dried using Na_2SO_4 and charcoal and evaporated to yield 3.70 g (51%) of a yellow liquid (bp. 80°/0.075 mm Hg). A sample was converted to the maleate salt using Et_2O:EtOH = 5:1, mp. 129-133°. ^{1}H NMR (free base, $CDCl_3$): δ 1.61 (s, 1H, exchanges with D_2O); 2.27 (t, 2H); 2.50 (t,

2H); 2.88-2.98 (t, 4H); 5.05 (s, 1H). ^{13}C NMR (free base, $CDCl_3$): δ 34.3 (t), 36.8 (t), 47.3 (t), 47.6 (t), 92.6 (d), 116.4 (s), 165.4 (s).

Anal. Calcd. for $C_7H_{10}N_2 \cdot C_4H_4O_4$: C: 55.46, H: 5.92, N: 11.76. Found: C: 55.44, H: 5.77, N: 11.66

2-[1-(1,1-Dimethylethyloxycarbonyl)piperidin-4-yliden]acetonitrile (5i).- A sodium hydride dispersion in paraffin (60%, 0.20 g, 5.0 mmol) was rinsed with petroleum ether (40-65°, 3 x 5 mL), suspended in 7.5 mL of dry DME, and cooled in an ice-bath. 0.89 g (5.0 mmol) of cyanomethylphosphonic acid diethyl ester[25] in 4 mL of DME was added at a temperature below 5°. After additional stirring at 10° for 15 min 1.00 g (5.0 mmol) of **4i**[27] in 7 mL of DME and 3 mL of dry methanol were added and the temperature adjusted to 5-10°. The reaction mixture was allowed to warm up to room temperature and, after stirring for 5 h, the mixture was cooled to 0° and treated dropwise with 12.5 mL of cold water. After 9h a crystalline precipitate had formed which was filtered off after addition of 16 mL of water, and dried *in vacuo* to yield 0.96 g (86%) of colorless crystals. Extraction of the filtrate with ethyl acetate (2 x 30 mL) gave, after recrystallization from diisopropyl ether, a second fraction of 0.1 g resulting in a total yield of 1.06 g (95%) of **5i**, mp. 117-119°. ^{1}H NMR ($CDCl_3$): δ 1.47 (s, 9H), 2.33 (t, 2H), 2.56 (t, 2H), 3.50 (t, 2H), 3.54 (t, 2H), 5.19 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 28.2 (q), 32.4 (t), 34.8 (t), 44.2 (2t), 80.1 (s), 94.2 (d), 116.0 (s), 154.2 (s), 163.3 (s).

Anal. Calcd. for $C_{12}H_{18}N_2O_2 \cdot 0.1\ H_2O$: C: 64.32, H: 8.19, N: 12.50. Found: C: 64.35, H: 8.03, N: 12.50

2-[(1-Triphenylmethyl)piperidin-4-ylidenacetonitrile (5j).- To a solution of 1.00 g (8.2 mmol) of **5h** and 2.34 g (8.4 mmol) tritylchloride in 20 mL of dichloromethane 4 mL of triethylamine were added dropwise. The resulting heterogeneous mixture was stirred for 1h at room temperature, diluted with 100 mL of ethyl acetate and extracted with water (5 x 20 mL). The organic layer was dried using Na_2SO_4 and evaporated to yield 3.5 g (appr. 100%) of crude **5j** as pale pink crystals. A small sample was recrystallized from cyclohexane, mp. 204-206°. ^{1}H NMR ($CDCl_3$): δ 2.34 (m, 4H); 2.50 (t, 2H); 2.73 (t, 2H); 5.01 (s, 1H); 7.12-7.35 (m, 9H); 7.47 (d, 6H). ^{13}C NMR ($CDCl_3$): δ 33.2 (t), 35.7 (t), 48.5 (t), 48.8 (t), 77.2 (s), 93.0 (d), 116.4 (s), 126.1 (d), 127.5 (d), 128.9 (d), 142.2 (s), 165.1 (s).

Anal. Calcd. for $C_{26}H_{24}N_2 \cdot 0.2\ H_2O$: C: 84.84, H: 6.68, N: 7.61. Found: C: 84.82, H: 6.65, N: 7.54

3-Methyl-2-buten-1-amine (6a).- A mixture of 111.0 g (482 mmol) of molten **3a** and 25 mL of DMF was added to 1.2 l of 3 N KOH in several portions during 30 min., resulting in an slightly exothermic reaction. After stirring at room temperature for additional 4 h the reaction mixture was extracted with ether (4 x 150 mL). The combined ethereal layers were extracted with brine (4 x 150 mL), dried over KOH and distilled using a 20 cm Vigreux column. The fractions boiling between 95 and 110° were collected, diluted using 100 mL of ether and this solution added in the course of 2 hrs. to a solution of 64 g (550 mmol) of maleic acid in 1.2 L of ether and 100 mL of methanol resulting in an exothermic reaction and reflux. The precipitation was completed by cooling 1 h at -30°. The product was filtered and dried *in vacuo* at 40°. Concentration of the filtrate gave a second fraction of the same purity resulting in a total yield of 77.3 g (80%) of colorless crystals. mp. 112-115°. A small sample was recrystallized from THF, mp. 115-116°. ^{1}H NMR ($CDCl_3$; free base): δ 1.33 (b, 2H), 1.60 (s, 3H), 1.69 (s, 3H), 3.23 (d, 2H), 5.22 (t, 1H); ($CDCl_3$; maleate): δ 1.63 (s, 3H), 1.71 (s, 3H), 3.41 (d, 2H),

5.19 (t, 1H), 6.03 (s, 2H), 7.0 to 8.5 (very broad, appr. 4H). ^{13}C NMR ($CDCl_3$; free base): δ 17.5 (q), 25.4 (q), 39.4 (t), 125.7 (d), 132.8 (s).

Anal. Calcd. for $C_5H_{11}N•C_4H_4O_4$: C: 53.72, H: 7.51, N: 6.96. Found: C: 53.95, H: 7.75, N: 6.93

2-Cyclopentylidenethanamine (6b).- Employing method A) described for **6c** using 5.36 g (50 mmol) of **5b** yielded 6.20 g (55%) yellow crystals of **6b** as the maleate, mp. (maleate) 141-145°. Method C) yielded 7.56 g (67%) at the same scale, bp. (free base) 80-90°/10 mm Hg. ^1H NMR (free base, $CDCl_3$): δ 1.25 (s, 2H), 1.50-1.70 (m, 4H), 2.10-2.25 (m, 4H), 3.12 (dt, 2H), 5.32 (m, 1H); (maleate, DMSO-d_6): δ 1.63 (m, 4H); 2.25 (m, 4H); 3.36 (d, 2H); 5.29 (m, 1H); 6.03 (s, 2H); 7.70 (b, 3H, exchange with D_2O). ^{13}C NMR (free base, $CDCl_3$): δ 26.0 (t), 26.1 (t), 28.3 (t), 33.4 (t), 41.0 (t), 121.3 (d), 144.1 (s); (maleate, DMSO-d_6) δ 5.6 (t), 25.6 (t), 28.3 (t), 33.2 (t), 38.0 (t), 112.2 (d), 136.0 (d), 150.4 (s), 167.4 (s).

Anal. Calcd. for $C_7H_{13}N•C_4H_4O_4$: C: 58.14, H: 7.54, N: 6.16. Found: C: 58.27, H: 7.39, N: 6.08

2-Cyclohexylidenethanamine[28] (6c).- *Method A) using $LiAlH_4$.* A solution of 5.00 g (41.3 mmol) of **5c** in 45 mL of dry ether was added to 38 mL (34.5 mmol) of 0.90 M $LiAlH_4$ in ether at a rate of 0.15 mL/min. After completion of the addition the mixture was allowed to stir for additional 10 h, cooled to 0° with an ice-bath and treated with 3.3 g (183 mmol) of water in 35 mL of THF at such rate that the temperature remained below 5°. The mixture was filtered and the solid washed thoroughly with ether (2 x 50 mL). The combined filtrates were dried (Na_2SO_4) and evaporated to yield 5.1 g of a yellow liquid. The crude product was dissolved in 50 mL of ether and added to a solution of 4.70 g (40.5 mmol) maleic acid in 50 mL of ether:methanol = 9:1, resulting in a strong reflux. The crystallization was completed in 1 h at -25°. The colorless crystals (6.30 g, 67%) of **6c** maleate were filtered and dried *in vacuo*.

Method B) using $LiAlH_4/AlCl_3$: 3.15 g (23.6 mmol) of $AlCl_3$ in 20 mL of dry ether were added to 26 mL (23.4 mmol) of a 0.9 M $LiAlH_4$ solution in ether keeping the temperature below 0° with an ice/salt bath. The mixture was allowed to warm up to room temperature and 3.00 g (24.8 mmol) of **5c** in 30 mL of dry ether were added at a rate of 0.15 mL/min. After stirring for additional 7 h at room temperature, the reaction mixture was cooled to 0° and treated with 2.0 g of water in 20 mL of THF, maintaining the temperature below 5° with an ice-bath. After stirring for 15 min. the precipitate was dissolved with 2N H_2SO_4 (pH = 2), stirred for 5 min and adjusted to a pH of 14 with 40% NaOH. The aqueous layer, which contained only small amounts of precipitate, was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were extracted with 20 mL of brine, dried using Na_2SO_4 and evaporated. The crude product (2.85 g yellow liquid; appr. 90% product) was converted to the maleate as described above, using 3.00 g (25.8 mmol) of maleic acid to yield 3.86 g (65%) of **6c** maleate as colorless crystals.

Method C) using AlH_3 ($LiAlH_4/H_2SO_4$): Concentrated H_2SO_4 (1.16 g, 11.85 mmol, p.A. Merck) was added dropwise to 26 mL (23.4 mmol) of 0.9 M $LiAlH_4$ solution in ether under cooling, keeping the temperature below 25°. After stirring for 30 min. 3.00 g (24.8 mmol) of **5c** were added at a rate of 0.15 mL/min and stirring at room temperature was continued for 9 h. The mixture was cooled in an

ice-bath to 0° and 2.0 g of water in 20 mL of THF were added, maintaining the temperature below 5°. 2N NaOH (appr. 3 mL) was added dropwise until the hydroxides formed a filterable precipitate, which was filtered and washed with ether (2 x 10 mL). The combined filtrates and washings were extracted with ether, dried over Na_2SO_4 and evaporated to yield 3.02 g of the crude product as a yellow oil. The crude product was converted to the maleate as described above using 3.00 g (25.8 mmol) of maleic acid to yield 3.17 g (57%) of colorless crystals, mp. 124-127° or distilled, bp. 80°/11 mm Hg. ^{1}H NMR (free base, $CDCl_3$): δ 1.1 (b, 2H); 1.5 (m, 6H); 2.05 (m, 4H); 3.2 (d, 2H); 5.15 (t, 1H). (maleate, $CDCl_3$+DMSO-d_6): δ 1.52 (m, 6H); 2.12 (m, 4H); 3.51 (d, 2H); 5.21 (t, 1H); 6.23 (s, 2H); 8.05 (b, appr. 4H). ^{13}C NMR (free base, $CDCl_3$): δ 26.6 (t), 27.7 (t), 28.3 (t), 28.5 (t), 36.8 (t), 38.6 (t), 122.7 (d), 140.7 (s).

Anal. Calcd. for $C_8H_{15}N•C_4H_4O_4$: C: 59.73, H: 7.94, N: 5.80. Found: C: 59.44, H: 7.86, N: 5.78

2-(4-t-Butylcyclohexylidene)ethanamine (6d).- Following method A) as described for **6c**, 4.43 g of **5d** yielded 4.46 g (appr. 80%) of the crude amine **6d** as a yellow oil which was converted to the maleate as described above, yielding 3.05 g (41%) of the maleate salt as colorless crystals, mp. 130-135°. ^{1}H NMR (maleate, DMSO-d_6): δ 0.83 (s, 9H), 0.9-1.3 (m, 3H), 1.55-2.30 (m, 5H), 2.63 (d, 1H), 3.42 (d, 2H), 5.11 (t, 1H), 6.02 (s, 2H), 7.70 (b, appr. 4H).

Anal. Calcd. for $C_{12}H_{23}N•C_4H_4O_4$: C: 64.62, H: 9.15, N: 4.71. Found: C: 64.43, H: 9.39, N: 4.69

E-4-(t-Butyldimethylsilyloxy)-3-methyl-2-buten-1-amine (6f).- A 0.9 M solution of $LiAlH_4$ (25 mL, 22.5 mmol) in ethyl ether was diluted with 40 mL of dry ether and treated dropwise with 1.10 g (11 mol) of concentrated sulfuric acid at 0°. The aluminum hydride solution was then allowed to warm to room temperature and 5.30 g (25 mmol) of **5f** in 40 mL of dry ether were added during 3 hrs using a syringe pump. After additional stirring at room temperature for 100 min the mixture was cooled to 5° and treated dropwise with 3 mL of water in 30 mL of tetrahydrofuran followed by 3 mL of 2N sodium hydroxide. The precipitate was filtered and washed with ether (3 x 20 mL). The combined filtrates and washings were dried (Na_2SO_4) and evaporated. Kugelrohr-distillation of the crude product (60-80°/0.004 mm Hg) yielded 2.6 g (51%) of **6f** as colorless liquid. ^{1}H NMR ($CDCl_3$): δ 0.08 (s, 6H); 0.92 (s, 9H); 1.57 (s, 3H); 3.29 (d, J = 6.8 Hz, 2H); 4.01 (s, 2H); 5.49 (tq, J_1 = 6.8 Hz, J_2 = 1.4 Hz, 1H).

2-(1-Triphenylmethylpiperidin-4-yliden)ethanamine (6j).- A solution of 4.30 g (1.17 mmol) of **5j** in 250 mL of dry ether was added to 40 mL of a 0.44 M $LiAlH_4$-solution in ether during 3 hours. After additional stirring for 8 h at room temperature 25 mL of a 0.44 M $LiAlH_4$-solution in ether was added and the mixture was stirred overnight. The turbid solution was cooled to 0° and 2.2 g of water in 30 mL of THF were added slowly, keeping the temperature below 5°. The precipitate was filtered, washed with ether (2 x 25 mL) and the combined organic phases were dried (Na_2SO_4) and evaporated. The crude product was purified by preparative chromatography (SiO_2, toluene + 7% of MeOH) to yield 1.32 g (30 %) of a colorless solid. An analytical sample was precipitated as maleate (194-196°, dioxane). ^{1}H NMR ($CDCl_3$): δ 2.20-2.50 (m, 8H); 3.16, 5.12 (t, 1H); 7.09-7.32 (m, 9H); 7.50 (d, 6H). ^{13}C NMR ($CDCl_3$): δ 29.0 (t), 36.4 (t), 37.5 (t), 49.0 (t), 49.6 (t), 77.2 (s), 119.6 (d), 125.8 (d), 127.3

(d), 129.0 (d), 140.7 (s), 142.7 (s).

Anal. Calcd. for $C_{26}H_{28}N_2 \cdot C_4H_4O_4 \cdot 1.5\ H_2O$: C: 74.36, H: 6.66, N: 5.78
Found: C: 70.45, H: 6.81, N: 5.44

Zeatin (8e).- The TBDMS-protected **8f** (100 mg, 0.3 mmol) was dissolved in 1 mL (0.5 mmol) of ice-cold 0.5 M sulfuric acid in methanol and stirred at room temperature for 2 h. The resulting precipitate of zeatin hydrogen sulfate (mp. 153-155°) was filtered and washed with methanol/ether (1:2). Workup of the mother-liquor yielded a total of 100 mg. This salt was dissolved in 1 mL of 8N ammonia in methanol, the precipitate of ammonium sulfate was filtered using filter-cell (Hyflo) and washed with methanol. Evaporation of the filtrate yielded 80 mg (84%) of **8e** as colorless crystals, mp. 204-207°. ^{1}H NMR ($CDCl_3$): δ 1.69 (s, 3H); 3.80 (d, 2H); 4.15 (b, 2H); 4.75 (t, 1H, exchanges with D_2O); 5.53 (t, 1H); 7.65 (b, 1H, exchanges with D_2O); 8.09 (s, 1H); 8.19 (s, 1H).

N-(*E*-4-[(1,1-Dimethylethyl)dimethylsilyloxy]-3-methyl-2-buten-1-yl-)purin-6-amine (8f).- A mixture of 6-chloropurine (0.50 g, 3.2 mmol), **6f** (0.80 g, 3.7 mmol), and 0.9 g (8.9 mmol) triethylamine in 40 mL of 1-butanol was stirred for 2 h at 50° and refluxed for additional 2 h. After evaporation of the solvent the residue was distributed between ethyl acetate and water (20 mL each). The aqueous layer was extracted with ethyl acetate (2 x 10 mL) and the combined organic layers were dried using Na_2SO_4 and charcoal and evaporated. Recrystallization of the crude product from diisopropyl ether yielded 0.75 g (70%) of **8f** as colorless crystals, mp. 170-180°. ^{1}H NMR ($CDCl_3$): δ 0.8 (s, 6H); 0.91 (s, 9H); 1.75 (s, 3H); 4.09 (s, 2H); 4.35 (m, 2H); 5.69 (t, 1H); 6.11 (b, 1H, exchanges with D_2O); 7.98 (s, 1H); 8.45 (s, 1H); (1H, exchanges with D_2O, extremely broad). ^{13}C NMR ($CDCl_3$): δ -0.2 (s); 13.5 (q); 18.2 (s); 25.8 (q); 38.1 (t); 67.5 (t); 119.2 (d); 137.7 (s); 138.9 (s); 149.1 (s); 152.3 (s); 154.6 (s); C-5 not detected due to slow relaxation.

Anal. Calcd. for $C_{16}H_{27}N_5OSi$: C: 57.62, H: 8.16, N: 21.00. Found: C: 57.50, H: 8.08, N: 20.86

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